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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/961,163	09/21/2001	Katherine E. Fisher	PC10667AGPR	4614

7590

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EXAMINER

QIAN, CELINE X

ART UNIT

PAPER NUMBER

1636

10

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/961,163

Applicant(s)

FISHER ET AL.

Examiner

Celine X Qian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 10-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☒ Claim(s) 9 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 September 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) Z.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

Claims 1-20 are pending in the application.

#### ***Election/Restrictions***

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that claims of Group II and III depends on the claim of Group I, hence a search of Groups II and III would overlap with a search of Group I. Applicants further argue that the gene-targeting vector of Group IV is very similar to the RKO clone recited in the method of Group I. As such, there is no burden to search all the groups. This is not found persuasive because the inventions of Groups I-IV are patentably distinct for reasons set forth of the record mailed on 2/11/03. A search of one group is not co-extensive with the search of another group, and a search of all the groups in a single application is burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 10-20 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-9 are currently under examination.

#### ***Specification***

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. For example, page 23, lines 10, 14 and 16. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

#### ***Claim Objections***

Claims 9 is objected to for being dependent on a rejected claim. It would be allowable if written in independent form.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6 and 7 rejected under 35 U.S.C. 102(b) as being anticipated by Nehls (WO 98/37175).

Nehls discloses a lambda KOS vector comprises a stuffer DNA flanked by restriction sites so that the stuffer DNA can be replaced by genomic DNA; an E. coli. origin of replication; an antibiotic resistance gene ( $\beta$ -lactamase gene); a yeast origin of replication (2 $\mu$ m); a selectable marker suitable for use in yeast (TRP1 gene); negative selectable markers suitable for use in mammalian cells (HSV-tk gene); a direct repeat of recombinase sequence (loxP) for conversion of the lambda phage vector into E. Coli/yeast shuttle plasmid (see page 8, 1<sup>st</sup> paragraph, and page 12-13, bridging paragraph). Nehls also disclose a positive selection cassette vector comprising a bacterial selection marker, a mammalian positive selection marker, a yeast selection marker and unique restriction sites flanking the positive selectable marker, and recombinant arms comprising 40 nucleotides that shares homology with the integration site of the genomic DNA, which can be generated by PCR (see page 8, 2<sup>nd</sup> paragraph, and page 13, 2<sup>nd</sup> paragraph, page 14, 2<sup>nd</sup> paragraph). Nehls further discloses that the generation of lambda phage library by inserting genomic DNA into KOS vector and replace the stuffer fragment, and infection of a Cre-recombinase expressing bacterial strain to convert the lambda vector into a E. coli/yeast shuttle vector pKOS (see page 12-13, bridging paragraph). This shuttle vector is co-transfected with a

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positive selection cassette (URA3/CAT-selection cassette) into yeast for inserting the positive selection marker into the genomic DNA by homologous recombination and selection for complementation of both auxotrophic requirements of the TRP/URA3-deficient yeast strain (page 13, 2<sup>nd</sup> paragraph). The plasmid is recovered from the yeast and transferred into E.coli which allows a further selection by plating on chloramphenicol and ampicillin containing plates using standard procedures, and the gene-targeting vector is finally recovered (page 14, 1<sup>st</sup> and 2<sup>nd</sup> paragraph). In summary, Nehls discloses a method of generating a gene-targeting vector for using in mammalian cells by homologous recombination in yeast. Therefore, Nehls discloses the instantly claimed invention.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nehls (WO 98/37175), in view of Lewin (textbook: Gene 4<sup>th</sup> edition).

The teaching of Nehls is discussed above. Nehls further teach that the lambda vector comprises two cos sites on left and right end of the phage for its packaging. However, Nehls does not teach that the vector is a cosmid clone.

Lewin teaches that cosmid vector is a plasmid vector has been modified by inserting cos sites, thus has the advantage of perpetuated in bacteria in the plasmid form, but can be purified by packaging *in vitro* into phages.

It would have been obvious to one of ordinary skill of art to use a cosmid clone comprise a cos site as the E. coli/yeast shuttle vector to use in the method of constructing a gene targeting vector as claimed because such clone have be able to propagate in bacteria and also be able to package into phages. One of ordinary skill in the art would have been motivated to do so for retaining the ability of the shuttle vector to be packaged into phage for purification *in vitro*. The level of skill in the art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill of art would have reasonable expectation to make a cosmid vector comprising a cos site and other claimed feature based on the teaching of Nehls. Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill of art at the time the invention was made.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nehls, in view of Brocard et al. (1997, PNAS, Vol.94, pp.14559-14563).

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The teaching of Nehls is discussed above. However, Nehls does not teach the positive selection cassette vector further comprises loxP or FRT sites flanking the positive selection marker.

Brocard et al. teach a method of spatio-temporally controlled site specific mutagenesis in the mouse by using inducible expression of Cre recombinase and loxP system (see abstract). Brocard et al. teach that by inserting loxP sites flanking the CAT selection marker, the spatio-temporally controlled Cre recombinase effectively removed selection marker and result in expression of lacZ in transgenic mouse (see page 14559, col.2, 2<sup>nd</sup> paragraph, and page 14560, 2<sup>nd</sup> col., 2<sup>nd</sup> paragraph).

It would have been obvious to one of ordinary skill of art to modify the selection vector taught by Nehls by inserting loxP sites to the positive selection cassette vector that flanks the selection marker to achieve temporal regulation in mammalian system as demonstrated by Brocard et al. The ordinary skilled in the art would have been motivated to do so to make a gene-targeting vector that not simply knocks out the gene of interest but can also do it in a controlled manner. The level of skill in the art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill of art would have reasonable expectation to make the claimed vector. Therefore, the invention would have been prima facie obvious to one of ordinary skill of art at the time the invention was made.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nehls, in view of Luo et al. (6,280,937).

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The teaching of Nehls is discussed above. However, Nehls does not teach the positive selection cassette vector further comprises an IRES that allows the translation of the positive selection marker in mammalian cells.

Luo et al. teach a shuttle vector comprising IRES in front of a GFP reporter (see Figure 1). Luo et al. teach that IRES elements functions as initiators of the efficient translation of reading frames, and greatly facilitates the selection of cell expressing peptides at uniformly high levels (see col.8, lines 49-53).

It would have been obvious to one of ordinary skill of art to modified the positive selection cassette taught by Hehls by inserting an IRES in front of the mammalian/bacterial selection marker to ensure the proper expression of the marker in mammalian cells. One or ordinary skill of art would have been motivated to do so because Luo et al. teach that such element greatly facilitates the selection of cell expressing the peptides at high levels. The level of skill in the art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill of art would have reasonable expectation to make the claimed vector, and use it in the claimed method. Therefore, the invention would have been prima facie obvious to one of ordinary skill of art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the



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organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.  
July 24, 2003

*Anne-Marie Falk*  
ANNE-MARIE FALK, PH.D.  
PRIMARY EXAMINER